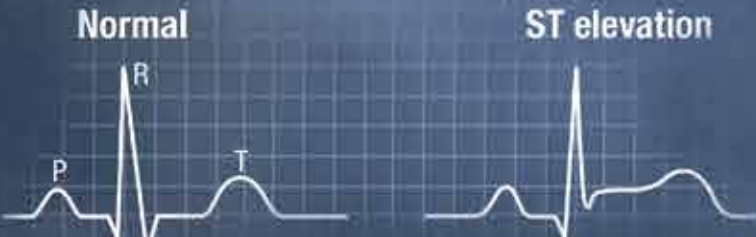


Healthy

Cellular uptake of lipids
Intracellular cholesterol metabolism
Reverse cholesterol transport

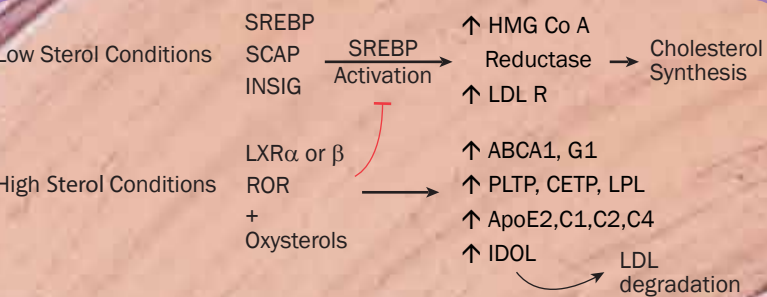
Endothelial Damage

Inflammation
LDL oxidation
Foam cell development



LDL OXIDATION		
Minimally modified (mmLDL) to oxidized (oxLDL)		
Agents	Substrates	Products
Lipoxygenase	ApoA1, ApoB	Aldehydes (HNE, MDA)
Myeloperoxidase	Cholesteryl esters	Free fatty acids
NADPH oxidase	Phospholipids	Lipid hydroperoxides
Phospholipases	Polyunsaturated fatty acids	Lysophosphatidic acid (LPA)
Xanthine oxidase		Lysophosphatidyl choline (LPC)
		TBARS

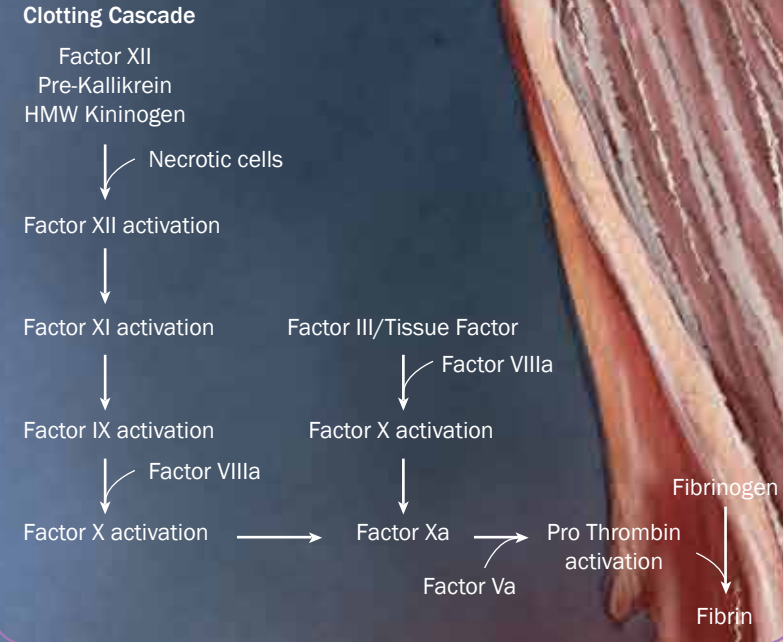
NITRIC OXIDE EFFECTS
↓ Vasoconstriction
↓ Endothelial permeability
↑ Angiogenesis
↓ Platelet aggregation
↓ SMC proliferation
↓ Leukocyte adhesion



HDL EFFECTS
↑ NO production
↓ NADPH oxidase
↓ Endothelial cell, macrophage apoptosis
↓ Leukocyte adhesion
↓ Monocyte activation
↓ Platelet aggregation
↓ Matrix degradation
• Removes oxidized lipids from LDL and cells
• Protects LDL from oxidative modification

ADVANCED GLYCATION END PRODUCTS (AGEs)
• Non-enzymatic conjugation of sugars to macromolecules
• Accelerated under hyperglycemic and oxidative conditions
• Increased production in diabetes and chronic inflammation

DYSFUNCTIONAL ENDOTHELIUM-DERIVED FACTORS
BMP-2, 4
CD2, 2.5
Crossveinless-2
CX3CL1
CXCL12, 3, 8
Endothelin-1
Endothelin-1
FGF basic
Follistatin
M-CSF
MMP-1, 3, 9
Noggin
Serpine E1/Pai-1
PDGF



PLATELET-DERIVED FACTORS
5-HT/serotonin
ADP/ATP/GDP
CXCL4, 7
Endostatin
Factors V, XI, XIII
Fas Ligand
Fibrinogen
Plasmin
Plasminogen
Polyphosphates
Protein S
Prothrombin
TFPI
Thrombospondin-1
Thromboxane A2
TRAIL
TWEAK
VEGF
vWF

CIRCULATING FACTORS
Adiponectin
↓ Leukocyte adhesion
↓ EC apoptosis
↓ Foam cell development
↓ Thrombosis
Leptin
↑ Leukocyte adhesion
↑ Platelet aggregation & activation
↑ Foam cell development
↑ SMC responsiveness to Arg II
IGF-1
↑ SMC proliferation
↑ NO production in EC
↓ ROS production in EC
• SMC apoptosis

RISK FACTORS FOR ATHEROSCLEROSIS
Advanced age
Diabetes
Genetics
↓ HDL cholesterol
High fat diet
Hypertension
↑ LDL cholesterol
Obesity
Sedentary lifestyle
Smoking

Plaque Rupture

Proteolytic thinning and rupture of fibrous cap
Thrombosis and arterial blockage
Aneurysm rupture

Plaque Progression

Foam cell accumulation and necrosis
Smooth muscle cell (SMC) proliferation and migration
Development of SMC cover and fibrous cap